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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,937	03/22/2001	Keith D. Allen	R-611	1801

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/05/2002 14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/815,937	Applicant(s) ALLEN ET AL.	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-16 and 25-58* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 25-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 11-16, 25-58 are pending in the application.

Claims 11-16 and 25-38 are withdrawn from consideration for being directed to non-elected subject matter. Claims 39-58 are currently under examination.

This Office Action is in response to the Amendment filed on 8/19/02.

The Amendment filed 8/19/02 (Paper No. 13) has been entered.

Response to Amendment

The rejection of claims 8 and 17-23 under 35 U.S.C. 112, first paragraph is moot in light of Applicants' cancellation of the claims.

The rejection of claims 1-4, 9, 10, 17, 18 and 20-24 under 35 U.S.C. 112, second paragraph is moot in light of Applicants' cancellation of the claims.

The rejection of claims 1-8 and 10 under 35 U.S.C. 103 (a) is moot in light of Applicants' cancellation of the claims.

The newly added claims 44-58 are rejected under 35 U.S.C. 112, first paragraph as discussed below.

The newly added claims 39-45, 47, 49, 53 and 55-58 are rejected under 35 U.S.C. 112, second paragraph as discussed below.

The newly added claims 39-43 are rejected under 35 U.S.C. 103 (a) as discussed below.

Claim 40 is objected to for reasons discussed below.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 44-58 rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 44-58 are drawn to a transgenic mouse comprising a disruption in a lymphoid specific GPCR gene and exhibits phenotype comprising cellular infiltration in lung, pancreas, stomach or liver; and a method of making said transgenic mouse, and knockout constructs for making said mouse. The specification fails to teach a specific use for the transgenic knockout mouse as claimed. The specification only teaches a method for identifying agents that modulate lymphoid specific GPCR expression or function. However, the specification does not teach a specific use for agents that modulate lymphoid specific GPCR expression or function. Furthermore, it is not known how to determine the expression or function of a gene that has already been knocked out. The specification further discloses that the transgenic mouse may be used as a model to treat diseases that are associated with a disruption in a lymphoid specific GPCR gene. However, the specification does not teach any disease associated with the disclosed phenotype. Therefore, the utility of the transgenic knockout mouse comprising a disruption in a lymphoid specific GPCR gene is lacking.

Claim Rejections - 35 USC § 112

Claims 44-58 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

This rejection is based on the utility rejection discussed above. Since the invention lacks utility, one skilled in the art would have to engage in undue experimentation to use the invention as claimed. If Applicants can provide sufficient evidence to overcome the utility rejection, the scope of enablement discussed below applies.

The specification supports the enablement of a homozygous lymphoid specific GPCR gene knockout mouse that **lacks production of functional lymphoid specific GPCR protein**, wherein the mouse exhibits cellular infiltration in the lung, pancreas, stomach, or liver, a method of making said mouse by introducing the knockout construct into embryonic stem (ES) cells, selecting ES cells comprising retina-specific nuclear receptor knockout construct, introducing said ES cells into blastocyst, and subsequently producing a transgenic knockout mouse, however, does not reasonably provide enablement for a transgenic mouse comprising any type of lymphoid specific GPCR protein, and a method of making said knockout mouse by introducing the knockout construct into any type of cell, or introducing ES cells directly into the pseudopregnant mouse.

The nature of the invention is a transgenic mouse comprising a disruption in a lymphoid specific GPCR gene and exhibits phenotype comprising cellular infiltration in lung, pancreas, stomach or liver; and a method of making said transgenic mouse. The specification discloses a method for generating said mouse by homologous recombination using a lymphoid specific GPCR-targeting construct (see page 54-60, examples 1-4). The specification further discloses that the homozygous knockout mice exhibit the phenotype comprising cellular infiltration in lung, pancreas, stomach or liver (see page 59-60, lines 30-36 and line 5-9).

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, col.1 1st paragraph, Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous retina-specific nuclear receptor knockout mouse as exhibiting cellular infiltration in lung, pancreas, stomach or liver. And the phenotype of a lymphoid specific GPCR knockout mouse is essential for the use of said mouse.

The specification discloses that the word "disruption" comprises altering or replacing a promoter, enhancer, or splice site of a target gene, and can alter the normal gene product by inhibiting its production partially or completely or by enhancing the normal product's activity (see page 5, lines 24-27). However, such a broad range of different types of "disruption" would not produce the phenotype as disclosed by the specification. The specification only discloses a mouse with two alleles of lymphoid specific GPCR gene disrupted by inserting a DNA sequence encoding a selection marker, where said mouse exhibits the phenotype comprising cellular infiltration in lung, pancreas, liver or stomach. Thus, the phenotype of a transgenic mouse comprising a "disruption," as defined by the specification, in lymphoid specific GPCR gene is unpredictable because only inactivating disruptions would produce the phenotype disclosed in the specification. Thus, the specification, in the instant case, is not enabling for transgenic knockout mice that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. One skilled in the art would have to engage in undue experimentation to make and use the invention commensurate in scope with these claims.

The specification teaches a method of making the retina-specific nuclear receptor knockout mouse by introducing the knockout construct into embryonic stem (ES) cells, selecting ES cells comprising lymphoid specific GPCR knockout construct, introducing said ES cells into blastocyst, introducing the blastocyst into a pseudopregnant mouse, and subsequently generates a transgenic knockout mouse. However, the specification does not support a method of making said mouse by introducing the knockout construct into any type of cells (claim 56). In addition, the specification does not support such method as to introducing ES cells directly into a pseudopregnant mouse (claim 31). The prior art does not teach such methods either. Therefore, one skilled in the art would have to engage in undue amount of experimentation to make and use the invention commensurate in scope with these claims.

This rejection may be overcome by amending the claims to recite only the transgenic knockout mouse that lacks production of functional lymphoid specific GPCR protein and exhibits the disclosed phenotype, recite ES cells in claim 56, and provide additional method steps in claim 44.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-45, 47, 49, 53 and 55-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 39-45, 47, 49, 53 and 55-58, the term "cellular infiltration" renders the claims indefinite because the nature of the cells that infiltrate the recited organs is unknown.

Regarding claims 39-42, the term "selectable marker" renders the claims indefinite because it is unclear how a selectable marker protein can be part of a vector construct. It is recommended to change the term to "selectable marker gene."

Claim Rejections - 35 USC § 103

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Schweickart et al. (1994, Genomics vol. 23, 643-650).

The claims are drawn to a lymphoid-specific GPCR gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in a lymphoid-specific gene. The recitation of "wherein the target construct when...exhibits cellular infiltration in lung, pancreas, stomach, or liver" defines the intended use of the knockout construct, which does not carry patentable weight.

Mansour et al. teach a strategy for targeted disruption of the hprt and proto-oncogene int-2 in mice embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from hprt and int-2 respectively, and a neo selection marker in between the two sequences (see page 350, figure

3). However, Mansour et al. do not teach how to make a lymphoid-specific GPCR gene target construct and knockout mouse.

Schweickart et al. teach the cloning of human and mouse lymphoid-specific GPCR gene EBI1. They provide the cloned coding sequence for lymphoid-specific GPCR gene (see page 645, figure 1). Schweickart et al. also teach that EBI1 is highly homologous to several members of the leukocyte chemotactic peptide receptor family and its expression is specific to lymphoid organs (see page 648, 1st col., 3rd paragraph). Schweickart et al. further teach that this receptor plays a role in lymphocyte growth, differentiation, activation, leukocyte trafficking, and in the extravasation of blood cells into sites of inflammation (see page 648, 1st col., last line, 2nd col., 4th paragraph, line 1-2).

It would have been obvious to one of ordinary skill in the art to make a lymphoid-specific GPCR construct to make a lymphoid-specific GPCR knockout mouse. The skilled artisan would have been motivated to knockout the function of lymphoid-specific GPCR gene in a mouse to study the role this gene plays in lymphocyte growth and regulation (see page 648, 1st col., last line, 2nd col., 4th paragraph, line 1-2), as suggested by Schweickart et al. The ordinary artisan would have had reasonable expectation of success because of the teachings of Mansour et al., who teach a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Schweickart et al., who teach the coding sequence of the mouse lymphoid-specific GPCR gene, and also teach the importance of this gene in regulating lymphocyte growth, differentiation, activation and migration. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim Objections

Claim 40 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The nature of the "selection marker" and the "screening marker" is unknown (what is the difference between them?). As such, claim 40 does not further limit the parent claim (39).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-Marie Falk

ANNE-MARIE BAKER
PATENT EXAMINER

Celine Qian, Ph.D.
November 4, 2002